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DOI: <https://doi.org/10.1007/s10143-009-0230-4>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-32690>

Journal Article

Published Version

Originally published at:

Baumann, F; Schmid, C; Bernays, R L (2010). Intraoperative magnetic resonance imaging-guided transsphenoidal surgery for giant pituitary adenomas. *Neurosurgical Review*, 33(1):83-90.

DOI: <https://doi.org/10.1007/s10143-009-0230-4>

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Received: 12 July 2009 / Accepted: 12 September 2009 / Published online: 13 October 2009
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Abstract Giant pituitary adenomas (GPAs), defined as ≥ 40 mm in one extension, present a challenging subgroup of pituitary adenomas in terms of radical tumor removal and complication rates. The potential impact of intraoperative magnetic resonance imaging (iMRI) is investigated in a consecutive series and the results compared to the literature. From November 2004 until February 2005, six (five male) patients were operated for GPAs via an iMRI-guided transsphenoidal approach in the PoleStar™ N20. Clinical, endocrinological, and neuroradiological outcomes (at 3 months and yearly postoperative over 4 years) were assessed. Mean age was 46 years (range, 34–60). All patients presented with preoperative visual field defects, five with pituitary failure. Five adenomas were clinically nonfunctioning, one was producing GH and TSH. Preoperative imaging showed invasion of the cavernous sinus in all and extension to the interventricular foramen in two patients (one with occlusive hydrocephalus). Resection was total in four and subtotal (small cavernous sinus remnants) in two patients, leading to transsphenoidal reoperation in one patient. Visual acuity and fields improved in all six patients. The patient

with occlusive hydrocephalus developed a postoperative cerebrospinal fluid leak (subsequently revised), two patients developed temporary, one permanent central diabetes insipidus, and one of them transient hyponatremia. Compared to the preoperative situation, endocrine status in the long-term follow-up (mean, 25 months) remained unchanged in four and worsened in two. Two patients were considered not to require hormone replacement therapy. IMRI supports transsphenoidal resections of GPAs because residual adenoma and related risk structures are easily detected and localized intraoperatively, extending the restricted visual access of the microscope beyond mere surface anatomy to a three-dimensional view. More radical removal of adenomas in a single surgical session combined with low complication rates are accomplished. This may add to a favorable clinical and endocrinological outcome in GPAs.

Keywords Giant pituitary adenoma · Intraoperative magnetic resonance imaging · Outcome · Transsphenoidal surgery

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Introduction

Giant pituitary adenomas (GPAs), which comprise a subgroup of pituitary adenomas (PAs), are inconsistently defined when it comes to size. Hardy's classification groups PAs into four types, according to qualitative extensions [11, 14]. Other authors define GPAs as tumors ≥ 30 mm in diameter [1, 8], as ≥ 40 mm in diameter [9, 10, 19], or as tumors extending more than 40 mm from the midpoint of the jugum sphenoidale or to within 6 mm of the interventricular foramen [7, 12, 18]. Patients with GPAs compared to patients with non-GPAs [8] more frequently

present clinically with visual symptoms and headaches than hormonal disturbances [1, 8, 9, 12, 14]. Most GPAs are non-secreting, followed by growth hormone (GH) secretion and prolactinomas [1, 8, 10, 12, 14]. Radiologically, these tumors show more aggressive behavior with cavernous sinus (CS), skull base, and paranasal sinus invasion. Invasion or infiltration is not confined to a selected adenoma size or diameter and varies according to literature from 9% to 40%, but is more prevalent with larger tumors [8, 16]. Additionally, GPAs can cause occlusive hydrocephalus by impairment of cerebrospinal fluid (CSF) drainage [12].

Gross tumor resection, thus, presents a challenge to the pituitary surgeon. Numerous strategies (transsphenoidal, transcranial, radiotherapy, or a combination of these) have been proposed [1, 14, 15], including insertion of a lumbar subarachnoid catheter for saline infusion to deliver the suprasellar tumor into the operative field by increasing intracranial pressure [20]. Especially CS infiltration often makes total resection demanding or impossible. Between 27.9% and 40% of tumors are excised totally according to several reports [1, 8, 9], and surgery can improve the primary symptom of the patient, diminished vision, in 65% to 90% [1, 9].

The most frequent postoperative complications include transient diabetes insipidus (DI) in 3.7% to 18.8% and CSF leak with meningitis in 7.4% to 14.6% [8, 9]. In one study, these complications were not significantly more frequent than in non-giant PAs [8]. Permanent DI or panhypopituitarism, third nerve palsy, and hemiparesis have been reported, as well as death from massive bleeding in 2.2% to 4.2% [8, 9].

Intraoperative magnetic resonance imaging (iMRI) has been used in the operating room for over a decade. As far as PAs are concerned, this imaging technique has led to a more radical one-stage resection of these tumors and to a decrease of perioperative morbidity and mortality [3, 5, 6, 13, 17], especially in macroadenomas with suprasellar extension [4].

We report our experience with the use of the iMRI in transsphenoidal surgery for GPAs, investigating the impact of this imaging modality on the amount of resection and complication rates, including long-term clinical, ophthalmological, endocrinological, and neuro-radiological follow-up.

Patients and methods

Patients with pituitary tumors ≥ 40 mm in one extension, who were operated in the PoleStar™ N20 (0.15 Tesla, Medtronic Navigation, Louisville, CO, USA) at the Department of Neurosurgery of the University Hospital of

Zurich, Switzerland, between November 2004 and February 2005, were included in the study. This sample represents a cluster of such patients during that time.

Preoperative assessment

Preoperative computed tomography (CT) and MRI scans of the sellar region were performed to determine bony structures as well as tumor configuration and localization of the normal gland and pituitary stalk. All patients had an endocrinological investigation for pituitary function as well as ophthalmological exams.

In all patients, an iMRI-guided endonasal-transsphenoidal approach was used. All operations were performed by the senior author (RLB).

Surgical technique

The patient is placed in a supine position with the head slightly reclined and fixed in an MRI-compatible head holder. The radio frequency coil is attached around the patient's head. To optimize imaging field and quality, the center of the two adjustable magnets must be brought at a level close to the center of the adenoma. In most patients, a bandage is applied over the shoulders with careful traction in a cranio-caudal direction to reach the most basal structures (sphenoid sinus and clivus). The magnet's position is tested by a 24-sec scan with 8 mm-slice thickness and T2-like specifications (e-steady sequence). The three-dimensional reconstruction allows immediate corrections of the magnet's position if necessary. Then a 7-min 4 mm-slice gadolinium-enhanced T1-weighted scan, which serves as baseline for neuronavigation, is performed. A self-retaining endonasal speculum is inserted typically in the contralateral nostril or in the nostril that corresponds to the more spacious intrasphenoidal sinus, and its anterior wall is displayed under the operating microscope. The nasal mucosa is incised on the sphenoid crest with a disk knife in an inverted T-shaped fashion, and the anterior wall of the sphenoid sinus is removed with punches or a chisel, depending on the thickness of the bone. The intrasphenoidal mucosa and septum are removed with rongeur forceps until the anterior wall of the sella turcica to its lateral borders is displayed. This wall is then opened by a chisel, and the dura is incised in an x-shaped fashion with a bayonet-handled scalpel. Using tumor grasping forceps, a suctioning device, and curettes of different sizes and shapes, the tumor is debulked in a stepwise fashion. Progress is verified by serial 3.5-min 4 mm-slice gadolinium-enhanced T1-weighted scans. Before a scan, a bone wax ball covered by a piece of a rubber glove is inserted in the region of the sella. This ball, which packs the region acting as a hemostatic by local compression, is

visualized as an easily detectable signal-void on MRI scans and facilitates the interpretation of the iMRI images. Blood appears homogeneously hyperintense, whereas residual adenoma has lower and more heterogeneous signal intensity. After tumor removal, the sella turcica and sphenoid sinus are packed with abdominal fat, covered with preserved bone fragments, and sealed by tissue adhesive if necessary (DuraSeal™, Confluent Surgical, Waltham, MA, USA). No nasal packing is used routinely.

Postoperative follow-up

On the first postoperative day, a CT scan of the sellar region was performed routinely for detection of postoperative complications. In the days following the operation, electrolytes and fluid balance were monitored twice a day (including daily weight) to detect DI or syndrome of inappropriate antidiuretic hormone (SIADH) secretion. The patients were asked to report any post-nasal drip (suggestive of CSF leak). Postoperative neuro-ophthalmologic exams were performed before the patients left the hospital.

Endocrinological follow-ups usually started at 1 month after discharge. Clinical, endocrinological, and neuroradiological outcomes were assessed 3 months postoperative and continued in yearly intervals. Resection was assessed as complete if imaging and endocrinological studies were inconspicuous in this regard, i.e., no residual tumor visible on MRI scans and, in active adenomas, no pituitary hormone hypersecretion detectable.

Results

In the 4-month period, six patients (five men and one woman) were included in the study. Age ranged from 34 to 60 years (mean, 46 years).

Preoperative findings

Visual disturbances were the leading symptom (100%) of the patients with GPAs. Fatigue was a complaint in two patients. Two male patients complained of sexual dysfunction. One patient presented with acromegaly. In one patient with sudden onset of extreme headaches and presumed subarachnoid hemorrhage, CT scan revealed pituitary hemorrhage in a sellar tumor. One patient showed memory deficits, urinary incontinence, and gait ataxia as primary symptoms, which led to cerebral imaging and identification of a large sellar mass with obstructive hydrocephalus (Table 1, Fig. 1).

Examination on admittance showed visual field defects in all patients: two had bitemporal hemianopia, three unilateral hemianopia, and one had bitemporal quadrantanopia. Preop-

erative endocrinological testing revealed a normal hormonal status in one patient and multiple hormonal insufficiencies in five patients (83%): all of them had gonadotropin (GT) deficiency (hypogonadism, with low GTs in the postmenopausal female and low testosterone in the four male patients), three had thyroid stimulating hormone (TSH) deficiency (central hypothyroidism, low fT4), and four adrenocorticotropin hormone (ACTH) deficiency (secondary adrenal failure, low cortisol); in one patient with insufficiency of the pituitary-adrenal axis but without central hypothyroidism and GH deficiency, a combined hyperthyroidism and excess of GH were found. The remaining five adenomas were clinically nonfunctioning adenomas (NFAs).

Preoperative imaging studies revealed invasion of the cavernous sinus in all and extension to the interventricular foramen in two patients, resulting in the aforementioned occlusive hydrocephalus in one patient.

Intraoperative findings

During resection of the adenoma, between two and six MR scans were performed; typically 3.5–7-min 4 mm-slice thickness gadolinium-enhanced T1-weighted scans. This led to a summarized scanning time of approximately 14 to 28 min. In all but one patient, intraoperative scans revealed residual tumor. Surgery was continued until no residual adenoma was visible on the MR scans (Fig. 2). Intraoperative debulking of the intrasellar part of the adenoma additionally revealed the pituitary stalk indicating the localization of compressed gland (pituitary stalk sign). Total surgery time, including intraoperative imaging, ranged between 2 and 4 h (mean 2.5 h).

Postoperative findings

All patients underwent iMRI-guided endonasal-transsphenoidal tumor extirpation. The immunohistochemical profiles of the NFAs were: luteinizing hormone (LH) and human chorionic gonadotropin (hCG) in three each, and ACTH in one. Tumor cells in one patient did not stain. All patients reported markedly improved vision immediately following surgery. The patient with preoperative hydrocephalus developed rhinoliquorrhea from CSF fistula and required revision and a ventriculoperitoneal shunt. Apart from that, there were no surgical complications. Postoperatively, two patients temporarily required desmopressin for central DI (an additional one permanently), one of them developed transient SIADH thereafter, which was treated with fluid restriction (Table 2, Fig. 3).

Compared to the preoperative hormonal status, at 1 month postoperative, one patient improved (from anterior pituitary insufficiency to only gonadotropin deficiency), one patient remained unchanged (anterior pituitary

Table 1 Patient characteristics, preoperative symptoms and signs, and adenoma features

Patient number	Sex	Age at diagnosis	Adenoma size and type	Additional neuroradiological findings	Preoperative symptoms	Preoperative signs	Preoperative hormonal status
1	F	60	50*45*34 mm Inactive	Occlusive hydrocephalus	Visual disturbance fatigue, gait disturbance, urinary incontinence, memory deficits	Left hemianopia, ataxia	GT deficiency
2	M	39	46*44*31 mm Active (GH, TSH)	None	Visual disturbance, sweating, tremor	Bitemporal hemianopia, acromegaly, intermittent cardiac arrhythmias	GH, TSH hypersecretion; ACTH, GT deficiency
3	M	36	50*50*50 mm Inactive	None	Visual disturbance (transient diplopia), sexual dysfunction	Bitemporal hemianopia	ACTH, GT, TSH deficiency
4	M	57	45*22*23 mm Inactive	None	Visual disturbance, fatigue, sexual dysfunction	Left hemianopia	ACTH, GT, TSH deficiency
5	M	51	56*36*39 mm Inactive	None	Visual disturbance	Left hemianopia	Normal
6	M	34	44*38*27 mm Inactive	Pituitary hemorrhage	Visual disturbance (diplopia), headache, nausea, vomiting	Bitemporal upper quadrantanopia	ACTH, GT, TSH deficiency

M male, *F* female, *ACTH* adrenocorticotrophic hormone, *GH* growth hormone, *GT* gonadotropin, *MRI* magnetic resonance imaging, *TSH* thyroid stimulating hormone

insufficiency), and four patients turned out worse (additional ACTH and TSH deficiency resulting in anterior pituitary insufficiency in one; additional gonadotropin deficiency in one; panhypopituitarism with newly developed ADH deficiency from anterior pituitary insufficiency in one; anterior pituitary insufficiency from normal hormonal status in one). As all patients at least had partial pituitary failure, all received hormone replacement accordingly.

Clinical follow-up at 3 months postoperative showed improvement of the preoperative symptoms (with hormone

replacement if necessary) as well normalization of the visual fields in all patients. Neuroradiological follow-up at 3 months postoperative showed total resection in four and subtotal resection in two patients with remaining tumor in the cavernous sinus (Fig. 3). Due to persistent elevation of insulin-like growth factor 1 (IGF-1)/GH, the patient with acromegaly was reoperated 5 months later.

Endocrinological follow-ups between 18 and 32 months postoperative showed further improvement in two patients (normal status in one; gonadotropin deficiency in a 60-year-old female) so that these were independent of hormonal

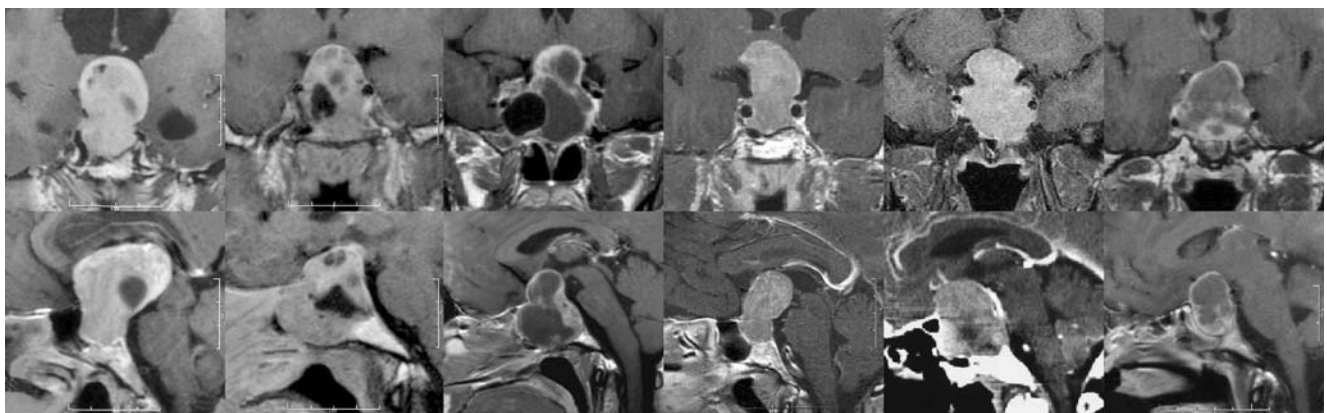
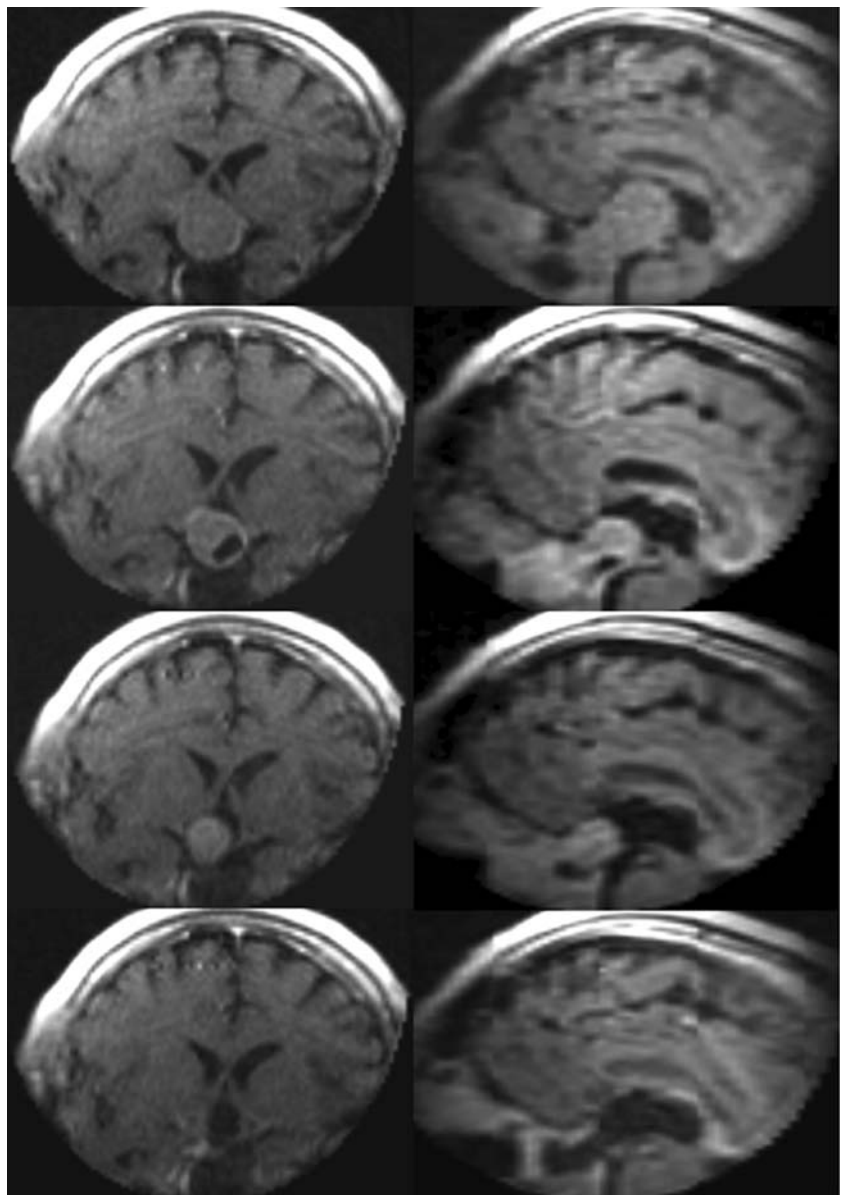


Fig. 1 Preoperative neuroradiological imaging studies (coronal section *above*, sagittal section *below*; each pair represents one patient, patient 1 on the left, patient 6 on the right; all are T1-weighted

gadolinium-enhanced MRI scans, except in patient 5, sagittal section is a CT scan with contrast media)

Fig. 2 Intraoperative consecutive T1-weighted gadolinium-enhanced MRI scans (coronal section on the *left*, sagittal reconstructions on the *right*) illustrating the gradual removal of the adenoma in a representative patient (patient number 4)



replacement therapy in the longer run. Two of the NFA patients (anterior pituitary insufficiency and panhypopituitarism, respectively) and the patient with GH/TSH secreting adenoma remained unchanged. One patient's endocrinological status worsened to an anterior pituitary insufficiency. Therefore, compared to the preoperative endocrinological situation, endocrine status in the long-term follow-up remained unchanged in four and worsened in two patients.

Additional neuroradiological follow-ups were performed in five patients between 15 and 46 months postoperative. These showed stable tumor in two with postoperative minimal residual adenoma in the cavernous sinus (questionable in one with normal endocrine status, possibly scar formation) and no recurrent tumor in the other patients

without residual adenomas. Due to persistent elevation of IGF-1 (low GH) and residual adenoma in the cavernous sinus, the acromegalic patient was evaluated for stereotactic radiosurgery.

Discussion

Giant pituitary adenomas are not unanimously defined in the literature concerning size (varying between ≥ 30 and >40 mm) [1, 7–12, 14, 18, 19]. In this study, PAs ≥ 40 mm in one extension were considered GPAs. Although it is questionable whether the largest diameter itself represents the grade of surgical difficulty, this definition seems practicable and is accepted in the literature. In our

Table 2 Surgical outcome, complications, and postoperative endocrinological and neuroradiological follow-up

Patient number	Gross resection and immuno-histochemical profile	Postoperative complications (measures)	1-month postoperative endocrinological follow-up	3-month clinical follow-up	3-month neuroradiological follow-up	Most recent endocrinological follow-up	Most recent neuroradiological follow-up
1	Total Negative	CSF leak (revision), transient DI (desmopressin)	GT, ACTH, TSH deficiency	Visual field normalization, preoperative symptoms', signs' improvement	No tumor residual	At 23 months: GT deficiency; ACTH, TSH normal	At 6 months: no tumor residual
2	Subtotal (CS rest), reoperation subtotal (CS rest) GH, TSH	None	IGF-1/GH, TSH hypersecretion; ACTH, GT deficiency	Visual field normalization, preoperative symptoms', improvement	Residual adenoma (CS)	At 32 months: IGF-1/GH, TSH hypersecretion; ACTH, GT deficiency	At 25 months: stable CS rest
3	Total LH, hCG, ACTH	None	ACTH, GT, TSH deficiency	Visual field, preoperative symptoms' normalization	No tumor residual	At 25 months: ACTH, GT, TSH deficiency	At 32 months: no tumor residual
4	Total LH, hCG	Permanent DI (desmopressin)	ADH, ACTH, GT, TSH deficiency	Visual field, preoperative symptoms' normalization	No tumor residual	At 18 months: ACTH, GT, TSH deficiency	At 46 months: no tumor residual
5	Subtotal (CS rest) HCG	Transient DI (desmopressin), transient SIADH (fluid restriction)	ACTH, GT, TSH deficiency	Visual field normalization	Residual adenoma (CS)	At 19 months: ACTH, GT, TSH normal	At 15 months: stable CS rest
6	Total LH	None	GT deficiency	Visual field, preoperative symptoms' normalization	No tumor residual	At 31 months: ACTH, GT, TSH deficiency	At 29 months: no tumor residual

ADH antidiuretic hormone, *ACTH* adrenocorticotrophic hormone, *CS* cavernous sinus, *CSF* cerebrospinal fluid, *DI* diabetes insipidus, *GH* growth hormone, *GT* gonadotropin, *hCG* human chorionic gonadotropin, *IGF-1* insulin-like growth factor 1, *LH* luteinizing hormone, *SIADH* syndrome of inappropriate antidiuretic hormone secretion, *TSH* thyroid stimulating hormone

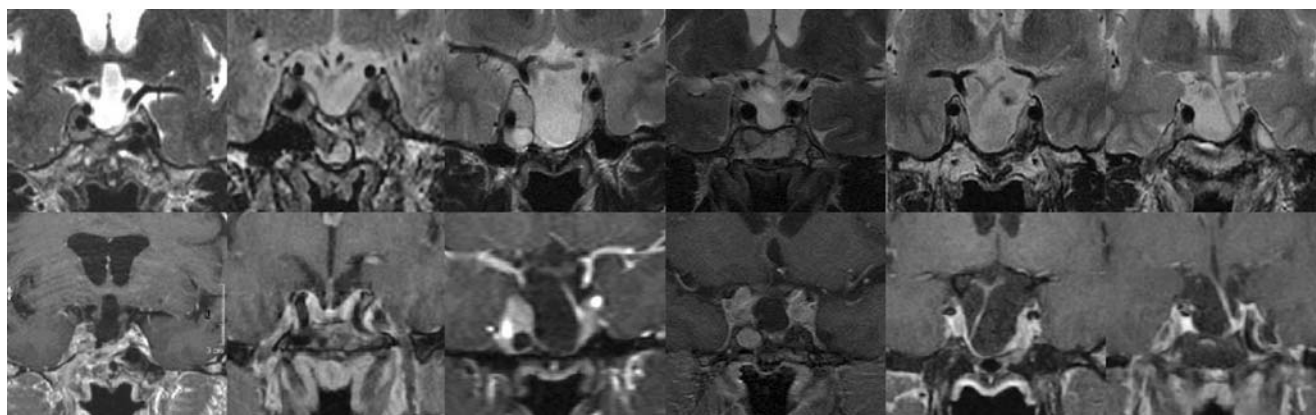


Fig. 3 Postoperative neuroradiological follow-up with MRI scans (T2-weighted coronal section *above*, T1-weighted gadolinium-enhanced section *below*; each pair represents one patient, patient 1 on the left, patient 6 on the right)

experience, invasion of the cavernous sinus and the middle cranial fossa present additional criteria that make radical resection demanding. Especially with CS involvement, in $\geq 60\%$ of cases only subtotal resection is accomplished [1, 8, 9]. Attempts to total extirpation result in high complication rates [8, 9]; therefore numerous strategies have been proposed to overcome the dilemma between radicality and safety [1, 14, 15, 20].

In 2004, Basso remarked that surgical treatment of nonfunctioning GPAs presented poor results because of the practical impossibility of radical tumor resection with consequent high recurrence rates [2].

Supplementary guidance by iMRI can improve tumor resection by presenting to the surgeon a three-dimensional visualization of the tumor and its residuals not directly accessible to the operating microscope or the endoscope, which both display mere surface anatomy. Especially in cases where residual adenoma is obscured by structures such as arachnoid pouches, with CS invasion, or in situations with pronounced hemorrhage, pathologic tissue is likely to be left behind, and iMRI is offering added value. With the support of fully integrated neuronavigation, tumor is localized and removed. In addition, the pituitary gland, which may often not be distinguished on diagnostic MRIs and in the operative field due to blood, can be identified on iMRI scans by following the direction of the stalk, which becomes visible in most cases, even after just partial debulking of the adenoma (pituitary stalk sign). We present a small sample of six patients with GPAs, which all were operated in a standardized endonasal-transsphenoidal way by the senior author (RLB) in the Polestar™ N20 between November 2004 and February 2005. The patients' characteristics as well as preoperative clinical and endocrinological symptoms are comparable with those patients presented in other GPA series (Table 1) [1, 8, 9]. MRI scans revealed invasion of the cavernous sinus in all patients (Fig. 1). All patients had clinical improvement of preoperative symptoms

and normalization of visual field deficits. Apart from one patient with postoperative CSF fistula (preoperative occlusive hydrocephalus), which required revision, there were no surgical complications, although a radical in four or almost radical resection in two patients was accomplished.

Compared to the preoperative situation (Table 2), endocrine status in the long-term follow-up (mean, 25 months) remained unchanged in four and worsened in two. Two patients gained independence of hormone replacement.

Long-term neuroradiological follow-up with serial MRI scans (mean, 26 months) showed stable tumor in two patients with postoperative CS rest and no residual or recurrent tumor in the others (Fig. 3), although in one patient with normal hormonal status, the CS enhancement could be related to scar formation (Table 2, Fig. 3).

Comparison with other series is difficult as only surgical outcome but no endocrinological complications or postoperative states (except for permanent DI) have been reported [1, 8, 9].

Nonetheless, we can report a much higher total resection rate of 66% (between 27.9% and 40% according to literature), accompanied by at least as favorable endocrinological outcome and symptom control as with conventional pituitary surgery [1, 8, 9].

Conclusions

We believe these favorable outcomes are supported by the use of intraoperative imaging, which serves as an intraoperative quality control to resection and to preservation of surrounding structures beyond that of the operating microscope or endoscope. This intraoperative information translates into more radical resections that may lead to fewer severe complications, fewer additional procedures (such as transcranial complementary operations, hormonal replace-

ment therapy, radiotherapy), and to reduction of overall costs of therapy of this difficult group of patients.

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Comments

Christopher Nimsky, Marburg, Germany

One of the major, widely accepted indications for intraoperative magnetic resonance imaging is the so-called “resection control” in surgery of pituitary adenomas. Intraoperative imaging acts as an immediate intraoperative quality control, unexpected postoperative findings are nearly excluded. Intraoperative imaging allows not only to increase the extent of a resection, but also to increase the percentage of complete removals.

The authors analyzed a special subset of pituitary adenomas undergoing transsphenoidal surgery, tumors with a diameter larger than 40 mm and could confirm the benefit of intraoperative imaging in these complicated cases. The suprasellar extent of resection in transsphenoidal surgery could be reliably assessed applying intraoperative low-field magnetic resonance imaging. However, the visualization of tiny intra- and parasellar structures will still be the domain of intraoperative high-field magnetic resonance imaging.

Moshe Hadani, Ramat Gan, Israel

Intra operative imaging becomes an integral part of image guided neurosurgery. The surgical approach to giant pituitary adenomas is a challenge. This paper describes the application of intraoperative MRI in the management of such tumors.

The number of patients is small, so statistical significant conclusions are not available, however, there is a trend towards more total and safer removal with the control by iMRI. It was previously shown in larger series that intraoperative imaging increased the rate of resection of pituitary macroadenomas of various dimensions. Transsphenoidal resection of pituitary adenoma is one of the surgical approaches which benefit a great deal from intraoperative imaging.

Hans Landolt, Aarau, Switzerland

The authors present a small series of six patients with giant pituitary adenomas over 4 cm in size operated on 2004–2005 through transsphenoidal microsurgical access using an intraoperative low magnet field mri “polestar”. All patients presented with visual deficits, and in four cases, with partial pituitary insufficiencies.

One case was acromegalic. In all cases, the tumor extended in the cavernous sinus. In two cases, a monro blockade was visible.

The surgical procedure described was the classical transsphenoidal microsurgical approach first standardized by J.Hardy, additionally guided by intraoperative navigation.

As innovation, the authors used intraoperative MRI imaging (iMRI) allowing adjusting navigation and surgical procedure to the actualized image information as already presented by them in abstracts since 1998.

The results are recovery of visual deficits in all cases and even endocrinologically stable function in four cases and worsening only in two cases after long-term follow-up, in spite of total removal of tumor in four cases and silent remaining in one. One case remained with diabetes insipidus. The acromegalic case was reoperated once more. One case showed CSF leak.

In contrast to the literature about giant pituitary adenomas operated without iMRI, this small series show excellent results. Beside the surgical competence of the senior author, his use of actualized intraoperative imaging helped decisively to attack tumor remnants specifically according to the new images. Any pituitary surgeon will be surprised to see unsuspected tumor remnants using an iMRI. To visualize and to be able to remove it during the same procedure are undisputable advantages especially in giant sellar tumors. Also, for smaller tumors iMRI helps to raise learning curves dramatically, allowing an immediate feedback of the aims achieved after each surgical step. The time needed for iMRI is irrelevant compared to the advantages offered, as we also experienced in Aarau since 2006. For transsphenoidal surgeons, an iMRI will become soon the golden standard as soon as larger series will be published.